

Plasma and urine aluminium concentrations in healthy subjects after administration of sucralfate

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1 Sucralfate (basic sucrose aluminium sulphate), a topical intestinal agent, was administered in suspension or granule form to 25 healthy subjects at a total dose of 4 g day⁻¹ for 21 days. Aluminium in plasma and 24 h urine samples was assayed before, during and after administration of sucralfate by inductively coupled plasma optical emission spectrometry.

2 Sucralfate produced significant increases in plasma and urine aluminium concentrations. On average, plasma aluminium increased from about 2 µg l⁻¹ to more than 5 µg l⁻¹ and 24 h urine aluminium increased from less than 5 µg to more than 30 µg. Both plasma and urine aluminium concentrations decreased rapidly after sucralfate was stopped. However, urinary aluminium concentrations remained higher than normal 5 and 10 days after discontinuation of sucralfate administration. Moreover subjects receiving sucralfate granules had significantly higher average urinary excretion of aluminium than subjects receiving the suspension.

3 The small but significant increase in plasma and urine aluminium following sucralfate administration in therapeutic doses may reflect intestinal absorption of aluminium. Although such absorption would appear to be moderate in healthy subjects, it is suggested that aluminium-based treatments should be used only intermittently, especially in patients with renal disorders.

Keywords aluminium sucralfate gastrointestinal absorption plasma concentration urinary elimination

Introduction

High aluminium concentrations are associated with encephalopathies appearing in patients with chronic renal failure undergoing haemodialysis (Alfrey *et al.*, 1976), and the principal cause of aluminium poisoning was shown to be the excess of aluminium in dialysis fluids (Allain *et al.*, 1978; Cartier *et al.*, 1978). These findings were confirmed when the removal of aluminium from dialysis fluids led to the disappearance of the encephalopathies. The oral ingestion of aluminium salts by patients under haemodialysis, in particular to reduce hyperphosphoraemia, can also lead to aluminium poisoning (Boukari *et al.*, 1978). A small proportion of the orally

ingested aluminium is absorbed from the gastrointestinal tract and, in the absence of renal excretion or elimination of aluminium by dialysis, aluminium accumulates in the body (Kaehny *et al.*, 1977; Recker *et al.*, 1977).

The urinary excretion of aluminium in subjects without kidney failure may reflect its gastrointestinal absorption. In the present study, healthy volunteers were given therapeutic doses of sucralfate in suspension or granule form for 3 weeks. The intestinal absorption of aluminium was evaluated by plasma and urine assays before, during and after administration of sucralfate.

Methods

After being fully informed about the nature of the study, 25 healthy volunteers agreed to participate. All were submitted to appropriate clinical examination and laboratory tests including full blood counts, plasma assays of electrolytes, glucose, creatinine and transaminases, and urine assays of proteins, glucose and ketone bodies.

Table 1 shows the distribution of subjects in two groups: Group I with 13 subjects (seven men and six women) and Group II with 12 subjects (six men and six women). One of the subjects in Group I was later excluded from the study because of an incomplete urine collection. Group I received sucralfate suspension while Group II received sucralfate granules at a total dose of 4 g day⁻¹ for 21 days. The sucralfate suspension (Batch 282 4060) was supplied in ready-to-use sachets containing 1 g of sucralfate made up to 5 ml. The sucralfate granules (Batch GW 20555-87) were supplied in sachets containing 1 g of sucralfate. Each subject took two sachets of sucralfate suspension or granules with a glass of water twice a day, 0.5 h before each morning and evening meal for 21 days.

Blood samples were obtained before breakfast on days D-7, D+1, D+7, D+15, D+27 and D+31. The blood was drawn into disposable plastic syringes, transferred to heparinized tubes and centrifuged immediately to obtain plasma

samples. Urine samples (24 h) were also collected on the same days. All plasma and urine samples were stored in aluminium-free plastic tubes or bottles at -20° C pending assay.

Aluminium assays were performed by inductively coupled plasma optical emission spectrometry using a Jobin-Yvon JY 48 Plus instrument according to a previously described technique (Allain & Mauras, 1979; Mauras & Allain, 1985).

The results of plasma and urine assays during administration of sucralfate on days D+1, D+7, D+15, D+21 and, after sucralfate was stopped, on days D+27, D+31, were compared with mean results for days D-7 before administration of sucralfate. The Wilcoxon test for paired values was used and the inter-group comparison was based on the Mann-Whitney test.

Results

Plasma aluminium concentrations before, during and after sucralfate administration to subjects in Group I, receiving sucralfate suspension, are shown in Table 2 while results for Group II, receiving sucralfate granules, are shown in Table 3. Before administration, plasma aluminium levels were below 5 µg l⁻¹ in both groups. During sucralfate administration, plasma aluminium concentrations increased

Table 1 Demographic data (mean ± s.d.)

	Sucralfate	Sex	Age (years)	Height (cm)	Weight (kg)
Group I	Suspension	6 M	29.3 ± 7.1	173.3 ± 5.6	70.5 ± 10.2
		6 F	24.8 ± 3.3	163.5 ± 9.2	54.3 ± 8.1
Group II	Granules	6 M	25.5 ± 4.6	181.3 ± 2.5	70.0 ± 4.9
		6 F	26.0 ± 3.0	162.7 ± 6.1	55.8 ± 5.4

Table 2 Plasma aluminium concentrations (µg l⁻¹) after administration of sucralfate suspension 4 g day⁻¹ for 21 days in Group I (12 subjects)

	Subject												Mean	s.d.	P value*
	1	2	3	4	5	6	7	8	9	10	11	12			
D-7	0.6	1.0	4.3	3.7	3.9	4.7	3.3	1.0	1.6	4.5	2.1	0.8	2.6	1.6	
D+1	3.4	0.4	7.2	6.4	6.2	4.5	5.5	6.1	3.6	0.0	6.5	3.0	4.4	2.4	0.05
D+7	5.9	1.7	1.4	5.2	4.6	8.6	3.6	3.0	5.0	7.7	7.2	7.7	5.1	2.4	0.01
D+15	2.8	0.9	2.2	5.9	7.0	5.0	1.1	7.6	2.5	4.2	7.5	2.4	4.1	2.5	NS
D+21	7.4	1.9	3.9	6.1	8.5	6.1	2.3	5.8	4.4	1.1	7.1	3.4	4.8	2.4	0.05
D+27	2.5	0.0	1.9	0.6	5.0	4.3	1.0	4.5	3.3	1.2	3.3	1.2	2.4	1.7	NS
D+31	0.2	1.3	1.4	0.7	4.6	4.8	0.4	4.1	3.3	0.0	4.5	1.0	2.2	1.9	NS

*P value compared with D-7.

Table 3 Plasma aluminium concentrations ($\mu\text{g l}^{-1}$) after administration of sucralfate granules 4 g day⁻¹ for 21 days in Group II (12 subjects)

	Subject														
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	s.d.	P value*
D-7	0.3	5.8	1.7	0.3	0.9	2.1	4.2	3.2	0.7	4.9	1.0	0.6	2.1	1.9	
D+1	2.5	3.8	5.4	5.0	3.9	9.6	4.0	2.9	12.5	4.4	4.1	1.3	5.0	3.1	0.05
D+7	3.8	5.2	3.9	3.2	3.7	25.7	6.3	6.0	13.8	4.8	10.3	2.9	7.5	6.6	0.01
D+15	3.5	5.0	15.4	3.1	3.8	21.4	13.1	3.6	18.0	8.5	6.1	1.9	8.6	6.7	0.01
D+21	0.0	6.3	5.2	3.1	2.4	13.5	39.8	5.7	18.3	12.6	1.4	1.6	9.2	11.2	0.01
D+27	2.5	2.1	2.4	1.9	0.7	4.0	3.2	0.6	2.7	2.2	1.5	2.3	2.2	1.0	NS
D+31	2.8	2.1	0.0	1.2	0.0	4.5	4.0	0.1	2.4	0.0	1.3	3.1	1.8	1.6	NS

*P value compared with D-7.

significantly though the difference was small and the mean values did not exceed $10 \mu\text{g l}^{-1}$. When sucralfate was stopped, all values returned to baseline.

Aluminium concentrations in 24 h urine samples before, during and after sucralfate administration to Group I and Group II are shown in Tables 4 and 5, respectively. Before administration, the aluminium concentrations were below $5 \mu\text{g}$ in both groups. During sucralfate administration, urine aluminium increased on D+1 to over $30 \mu\text{g}$ in Group I and to over $50 \mu\text{g}$ in Group II. Large individual variations in urine aluminium were observed, for example in subject 10 (Table 4) with $636 \mu\text{g}$ of urine aluminium on D+7 and in subject 6 (Table 5) with $1317 \mu\text{g}$ of urine aluminium on D+15. Throughout the period of sucralfate administration, on D+15 and D+21, Group II, receiving the granules, had a significantly higher average urinary excretion of aluminium than Group I, receiving the suspension, suggesting that sucralfate is more readily absorbed in granule form than in suspension. After sucralfate was stopped, the urinary recovery of aluminium decreased to values close to but higher than baseline.

Discussion

Plasma aluminium concentrations in the healthy volunteers before sucralfate administration were similar to those reported by others (Alderman & Gitelman, 1980; Brown *et al.*, 1984; Guillard *et al.*, 1984; Kostyniak, 1983; Oster, 1981; Versieck & Cornelis, 1981). A value of less than $5 \mu\text{g}$ for 24 h urinary excretion of aluminium was comparable with our previous findings ($6.4 \pm 4.5 \mu\text{g}$ (Mauras *et al.*, 1982) and $7.8 \pm 3.2 \mu\text{g}$ (Mauras *et al.*, 1983)) and with

those of others ($3 \pm 16 \mu\text{g}$ (Kaehny *et al.*, 1977) and $2.7 \pm 2.0 \mu\text{g}$ (Haram *et al.*, 1987)).

The administration of sucralfate suspension or granules at a dose of 4 g per day resulted in a significant increase in plasma aluminium concentration. This finding is in agreement with results reported by Pai *et al.* (1987). In our study the mean values of plasma aluminium did not exceed $10 \mu\text{g l}^{-1}$, a level that has until recently been considered as a normal value. The increase in plasma aluminium is quite small and this may explain why it was missed by some authors (Kinoshita *et al.*, 1982).

The urinary excretion of aluminium increased considerably following sucralfate administration. Although individual variation was great, the average values were comparable with those reported by Kaehny *et al.* (1977) after administration of aluminium phosphate, a salt that is considered to be very poorly absorbed by the intestinal tract. Urinary aluminium excretion was higher in subjects taking sucralfate granules than in subjects on sucralfate suspension. This may reflect greater gastrointestinal absorption of sucralfate from granules than from suspension. Two of our assays of 24 h urine gave extremely high aluminium values ($636 \mu\text{g}$ and $1317 \mu\text{g}$). These may be due either to contamination, the source of which we were unable to determine, or more likely to high gastrointestinal absorption. Some predisposing factors for increased aluminium absorption, such as acidification or high citrate levels (Kirschbaum & Schoolwerth, 1989; Slanina *et al.*, 1986) have been identified but we found no evidence of these in our subjects.

In conclusion, the administration of sucralfate in healthy subjects produces a small but significant increase in plasma aluminium concentration and a somewhat greater increase in urinary aluminium excretion. These increases are presumed to reflect gastrointestinal absorption of aluminium. The results obtained with

Table 4 Urinary excretion of aluminium ($\mu\text{g } 24 \text{ h}^{-1}$) after administration of sucralfate suspension 4 g day^{-1} for 21 days in Group I (12 subjects)

	Subject												Mean	s.d.	P value*
	1	2	3	4	5	6	7	8	9	10	11	12			
D-7	6.0	3.4	0.7	0.0	0.1	2.4	5.2	4.9	4.1	4.0	1.2	6.6	3.2	2.3	
D+1	25.7	33.6	41.2	19.9	55.3	45.1	44.3	30.3	13.3	59.7	63.0	4.2	36.3	18.5	0.01
D+7	60.0	19.6	12.2	33.9	42.7	91.6	60.9	50.8	23.6	636.0	142.6	33.6	100.6	172.4	0.01
D+15	39.0	23.1	17.0	31.8	33.3	12.5	38.4	62.2	21.6	67.6	95.4	24.8	38.9	24.4	0.01
D+21	129.8	20.4	8.4	18.1	88.2	5.0	28.6	56.1	23.1	59.1	42.0	35.7	42.9	36.2	0.01
D+27	11.8	7.9	3.7	1.1	7.1	4.1	7.3	11.2	8.2	13.6	69.4	13.4	13.2	18.1	0.01
D+31	7.8	3.2	2.7	0.6	4.3	5.4	5.9	4.2	4.2	4.7	18.1	7.1	5.7	4.4	0.02

*P value compared with D-7.

Table 5 Urinary excretion of aluminium ($\mu\text{g } 24 \text{ h}^{-1}$) after administration of sucralfate granules 4 g day^{-1} for 21 days in Group II (12 subjects)

	Subject												Mean	s.d.	P value*
	1	2	3	4	5	6	7	8	9	10	11	12			
D-7	2.2	0.6	0.0	3.5	0.5	1.9	7.0	1.5	7.5	0.4	2.6	1.2	2.4	2.5	
D+1	27.9	113.7	84.7	44.2	11.2	74.4	46.6	23.1	98.9	26.2	41.3	35.9	52.3	32.7	0.01
D+7	140.4	138.7	48.1	32.0	59.4	392.6	254.9	83.6	230.2	56.0	97.3	36.0	130.8	110.2	0.01
D+15	83.6	73.3	60.5	8.8	70.5	1317.0	360.7	114.2	195.5	282.1	48.5	12.5	218.9	362.3	0.01
D+21	117.9	108.3	53.6	44.8	40.5	252.9	417.2	184.4	130.8	601.0	84.9	4.5	170.1	176.5	0.01
D+27	10.2	13.9	19.9	2.1	8.4	19.6	19.9	12.9	21.1	18.5	11.2	9.1	13.9	6.0	0.01
D+31	2.8	11.4	3.9	1.4	6.6	10.5	21.8	13.9	20.8	8.8	12.7	11.5	10.5	6.4	0.01

*P value compared with D-7.

sucralfate are comparable with those described for aluminium phosphate, a salt that is considered to be poorly absorbed in the gastrointestinal tract.

From a practical point of view, even in the absence of renal failure and obviously if that is the case, it seems safer to prescribe aluminium

salts that are the least absorbed, provided of course that their therapeutic value is well established. Moreover, we suggest that aluminium preparations should be used intermittently.

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